Stille, Suzuki, and Sonogashira Couplings

Cross-Coupling reactions:

\[ \text{R-X} + \text{R'-M} \xrightarrow{\text{catalyst}} \text{R-R'} + \text{M-X} \]

R, R' are usually sp² hybridized
X = I (best), OTf, Br, Cl
M = Sn, B, Zn, Zr, In
Catalyst = Pd, sometimes Ni

Example:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Br} \quad + \\
\text{Ph-SnBu}_3 & \quad \xrightarrow{\text{Pd(0)}} \\
\text{H}_3\text{C} & \quad \text{Ph} \quad + \\
& \quad \text{Bu}_3\text{SnBr} \\
\end{align*}
\]

Mechanism:

\[
\begin{align*}
\text{Pd(II)} & \quad \xrightarrow{\text{reductive elimination}} \\
\text{Pd(0)L}_n & \quad \xrightarrow{\text{oxidative addition}} \\
\text{Bu}_3\text{SnBr} & \quad \xrightarrow{\text{transmetallation}} \\
\end{align*}
\]

Stille Reaction
General Cross-Coupling Reactions

Oxidative addition initially gives rise to a cis complex that rapidly isomerizes to a trans complex:

\[ \text{R-I} \xrightarrow{\text{PdL}_2} \text{L-Pd-I} \xrightarrow{\text{fast}} \text{R-Pd-I} \]

β-hydride elimination occurs for Csp\(^3\) halides other than methyl:

\[ \text{H} \underset{\text{Pd(II)L}_nX}{\text{Pd(II)L}_2X} \xrightarrow{\text{HPd(II)L}_2X} + \]

Both oxidative addition and reductive elimination occur with retention of double bond configuration.

Transmetallation is usually the rate-determining step, except where poor halide leaving groups (Cl) are used; then oxidative addition is RDS.

Order of ligand transfer from Sn:

\[ \text{alkyl} > \text{benzyl} > \text{alkenyl} > \text{aromatic} > \text{alkyne} \]

Stille-specific conditions:

**Catalyst:** Pd(PPh\(_3\))\(_4\), Pd(OAc)\(_2\), Pd\(_2\)(dba)\(_3\)

Large rate enhancements are often observed with poorly electron donating ligands: (furyl)\(_3\)P, Ph\(_3\)As

Cul can dramatically increase the reaction rate due to copper’s free-ligand scavenging ability:

\[ \text{Cul} \]

**JOC, 1994, 5905.**
Stille Cross-Coupling

The use of aryl chlorides requires special conditions:

Sn→Cu transmetallation increases the rate of cross-coupling reaction:

Coupling of Acid Chlorides:

Benzylic coupling:
Examples:

- Alkenes as coupling partners:

\[
\text{OTIPS} + \text{OTBDMS} \xrightarrow{\text{Pd}_{2} \text{(dba)}_{3} \text{ (20 mol %)} \atop \text{CdxCl} (1.8 \text{ equiv}) \atop \text{ } \atop \text{ -Pr}_{2} \text{NET, NMP} \atop \text{ } \atop \text{40°C, 53 h}} \frac{69\%}{\text{SNBu}_3} \]

\[
\text{N(CH}_3_2) \xrightarrow{\text{Pd(FPh}_3)_4 \text{ (10 mol %)} \atop \text{LiCl, THF} \atop \text{ } \atop \text{80°C, sealed tube}} \frac{100\%}{\text{Jatrophone}}
\]

\[
\text{(-)A83543A, (-)-Leptodin}
\]

- CdCl\textsubscript{2} serves as a transmetalation cocatalyst. Without it, homodimerization of both coupling partners was observed.


\[
\text{Pd(FPh}_3)_4 \text{ (10 mol %)} \atop \text{DMF, 23°C, 72 h} \frac{61\%}{\text{Indanomycin (X-14547A)}}
\]


1. \((\text{t-furyl})_{2} \text{PdCl}_{2} \text{ (20 mol %)} \atop \text{ -Pr}_{2} \text{NET, DMF, THF, } 33\text{°C, 7 h} \frac{74\%}{\text{}}

2. TBAF, AcOH, 0°C

3. H\text{F-Py, Py, THF, 23°C} \frac{61\%}{\text{}}


Andrew Haldie
Preparation of Aryl and Vinyl Stannanes

From Organolithium reagents via directed ortho-lithiation:

1. $t$-BuLi
2. Bu$_3$SnCl


Prep of vinyl stannanes:

$\text{Bu}_3\text{SnH} \quad \text{AIBN}$

$\text{Bu}_3\text{Sn}$ + $\text{Bu}_3\text{Sn}$

85 : 15

*a radical reaction, reversible, giving a thermodynamic ratio of products*

JACS, 1976, 222.

Alternatively,

$\text{Bu}_3\text{Sn}$ $\quad \text{Bu}_3\text{Sn}$

$\text{Bu}_3\text{Sn}$ $\quad \text{Bu}_3\text{Sn}$

69%

Synlett, 1997, 771.
Alternative Preparations of Vinyl Stannanes

Vinyl stannanes react cleanly with iodine to form vinyl iodides with retention of stereochemistry:

JACS, 1998, 3935
**Suzuki Coupling**

Suzuki Coupling is the reaction of vinyl or aryl boronic acids with aryl and vinyl halides or triflates using a palladium catalyst. Example:

\[
\text{Ph-B(OH)}_2 + \text{CHO} \xrightarrow{\text{Pd(OAc)}_2 (0.3 \text{ mol} \%)} \xrightarrow{\text{Na}_2\text{CO}_3 (1.2 \text{ eq})} \xrightarrow{\text{iPrOH, H}_2\text{O}} \xrightarrow{\text{heat}} \text{HOC-Ph-Ph}
\]

Mechanistic difference with Stille Coupling: Boron “ate” complexes are involved in transmetallation:

\[
\text{RL}_2\text{Pd–X} \xrightarrow{\text{HO}^-} \text{RL}_2\text{Pd–OH} \xrightarrow{\text{ArB(OH)}_2} \text{RL}_2\text{Pd-} \text{Ar} \text{B(OH)}_2
\]

The additive thallium hydroxide (TlOH) accelerates the rate of coupling by facilitating hydroxyl-halogen exchange at Pd: *JACS*, 1987, 4756.

Again Oxidative Addition and Reductive Elimination occur with retention of configuration

Reactivity of Leaving Groups: I > OTf > Br > Cl

Rates of reductive elimination: aryl-aryl > alkyl-aryl > alkyl-alkyl
Transfer of primary alkyl groups utilizing the Suzuki coupling:

\[
\text{FeCN} \quad 9\text{-BBN} \quad \begin{array}{c}
\text{9-BBN} \quad \text{B} \quad \text{CN} \quad \text{CN} \\
\text{PdCl}_2(dppf) \quad \text{K}_2\text{CO}_3 \\
\text{DMF, THF, 50°C}
\end{array} \quad \text{JACS, 1989, 314}
\]

large "bite" angle of dppf is believed to furnish a catalyst with a more favorable ratio of rate constants for reductive elimination vs. β-hydride elimination

\[
\text{JACS, 1984, 249}
\]

Buchwald's room temperature cross-coupling of Aryl chlorides:

\[
\text{MeO} \quad \begin{array}{c}
\text{Cl} \\
\text{P(t-Bu)}_2
\end{array} \quad \begin{array}{c}
\text{Pd(OAc)}_2 \text{ 1mol%} \\
\text{KF (3 eq), THF}
\end{array} \quad \begin{array}{c}
\text{P(t-Bu)}_2 \quad \text{2 mol%}
\end{array} \quad \text{ACIEE, 1999, 2413}
\]

Synthesis of Boronic Acids

1. $\text{B(Oi-Pr)}_3$
2. $\text{HCl/Et}_2\text{O}$

$\text{B(OiPr)}_2$

$\text{O}_2\text{N-OTf}$

$\text{PdCl}_2(\text{dppf})$ 3 mol%
$\text{KOAc}$, DMSO, 80°C

$\text{O}_2\text{N-BO}_2$

86%

$\text{H}_2$, Lindlar

$\text{B(OiPr)}_2$

$\text{TL, 1988, 2631, 2635.}$

$\text{JACS, 1972, 4370}$

$\text{syn-hydroboration}$

Comparison of the Stille and Suzuki couplings

The two methods are comparable, but the higher cost and toxicity of stannanes makes the Suzuki preferable.

When alkyl boranes and stannanes are in the same molecule, the organoboron group reacts preferentially under basic conditions.

Recently, triorganoindium reagents have been found to cross-couple with aryl and vinyl halides in an Atom-efficient manner, transferring all three organic ligands from indium. Indium is environmentally benign.
Sonogashira Coupling

Sonogashira Coupling is the coupling of terminal alkynes with aryl and vinyl halides in the presence of a palladium (0) catalyst, a Cu(I) co-catalyst, and an amine.
Examples of Sonogashira Coupling

TL, 2002, 4703

JOC, 2001, 6037